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Role of Positron Emission Tomography in Determining the Extent of CNS Ischemia in Patients With Sickle Cell Disease

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Nearly 25% of patients with sickle cell disease (SCD) experience central nervous system morbidity involving both large and small vessel disease. Optimal imaging methods for determining the extent of ischemia are not known. Positron emission tomography (PET) has the unique ability to show tissue function as well as structure. Reports concerning patients with non-SCD neurodegenerative disorders suggest PET may be useful in determining prognosis. We compared magnetic resonance imaging, magnetic resonance angiography, and neuropsychological testing with PET prospectively. Six patients with SCD and a history of stroke, aged 10 to 28, were enrolled. PET studies were performed on an ECAT HR 47 scanner (Siemens/CTI, Knoxville, TN) using 18-F-fluorodeoxyglucose as a tracer. PET interpretations were conducted in blinded fashion. MRI studies found two patients with only small vessel disease and four with both large and small vessel disease. In two of four subjects with large vessel disease, PET showed a corresponding metabolic abnormality and also identified an area of hypometabolism extending beyond the anatomical lesion as shown by MRI. PET did not demonstrate an abnormality corresponding with small vessel disease. Detailed neuropsychological testing demonstrated cognitive dysfunction in all cases. For some patients, PET may add sensitivity in detecting impaired metabolism in the area surrounding a major vessel infarct. However, the technique does not appear to be generally useful in characterizing small watershed or deep white matter infarcts. Larger studies, to include control subjects and carefully selected untransfused SCD patients, are needed. A combination of conventional imaging and neuropsychological testing remains the preferred evaluation for most SCD patients with neurologic symptoms. Am. J. Hematol. 60:268–272, 1999.

Key words: sickle cell disease; positron emission tomography; stroke; cerebrovascular disease; magnetic resonance imaging; magnetic resonance angiography

INTRODUCTION

The neurologic complications of sickle cell disease (SCD) are common and debilitating. They include a spectrum of large and small vessel disease, hemorrhage and atrophy [1]. A recent report from the Cooperative Study of Sickle Cell Disease (CSSCD) measured the prevalence and incidence of stroke in an unselected population of 4,082 patients as 3.75% and 0.46 events per 100 patient-years, respectively [2]. Similar observations have been reported from single institution studies in Philadelphia [3] and Jamaica [4]. Ascertaining cases by magnetic resonance imaging (MRI) surveillance of the population at risk rather than by occurrence of clinical neurologic events, Moser et al. [5] recently found a much higher prevalence. In this report, brain MRIs, were obtained between the ages of 6 and 14 years on 315 patients

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and subjected to blinded central review. The prevalence of infarction, ischemia, or atrophy was 22%. Thirteen percent of the subjects had anatomic abnormalities even in the absence of any overt neurologic findings. Though the prevalence of abnormal scans did not increase with age, the average number of lesions did, suggesting that progressive brain injury was occurring among affected individuals. When Armstrong and colleagues [6] performed neuropsychological assessment comparing patients with history of stroke and those having clinically silent MRI abnormalities to unaffected SCD controls, both groups were shown to have significant cognitive deficits. Neuropsychological deficits became apparent only with specific testing, often prompted by a decline in school performance. Thus, not only is the neurological morbidity of SCD more common than previously documented, it is also more subtle and more pervasive; methods for early evaluation and effective treatment are needed.

Several techniques are being evaluated for their ability to assess the risk of stroke or detect a subtle neurologic abnormality early in its evolution. Measurement of intracranial arterial blood flow velocity by Doppler ultrasound has achieved success in identifying patients at high risk for stroke [7]. Quantitative MRI [8] and proton MR spectroscopy [9] have also received recent attention in patients with SCD but a representative experience has yet to accrue. Positron Emission Tomography (PET) is a unique imaging method which holds promise in this regard. By utilizing a metabolically active tracer molecule, labeled with a positron emitting isotope, PET can provide information concerning both structure and function of tissue [10]. Examination of adults with Alzheimer's dementia [11] or anoxic brain injury [12] has suggested a potential role for PET in early detection and prognosis, respectively. A small study of neurologically normal patients with SCD suggested PET may be able to identify presymptomatic frontal lobe hypometabolism [13].

To determine the utility of PET imaging in the characterization of stroke among SCD patients, we compared MRI, magnetic resonance angiography (MRA), and neuropsychological testing with PET in a group of six patients with SCD and a history of overt neurologic dysfunction.

METHODS AND MATERIALS

Patients

Six patients with a history of clinically evident stroke were selected from the patient population of the Comprehensive Sickle Cell Disease Treatment and Research Center at Children's Hospital Oakland. All patients were of SS genotype. Their ages ranged from 10 to 29 years. Imaging and neuropsychological studies were obtained over intervals ranging from 7 to 59 months. All patients were on chronic transfusion when studied. The protocol was approved by the Research Committee and the Institutional Review Board at Children's Hospital Oakland and at Lawrence Berkeley Laboratory. All patients, or legal guardians, gave written informed consent to participate.

Imaging Studies

Subjects were studied using the Siemens ECAT EXACT HR 47 (Siemens/CTI, Knoxville, TN) following an injection of approximately 5–10 mCi of 18-F-fluorodeoxyglucose. Arterial catheterization for determination of a blood input function was not performed. Subjects were studied in the awake, eyes-open, ears-unoccluded position. Images were acquired over a period of 30 min and corrected for attenuation with a 40 min transmission scan. Magnetic resonance studies were obtained on a commercially available scanner at 1.5 Tesla field strength. Interpretation and comparison of PET and MRI images were conducted in blinded fashion by one investigator experienced in the interpretation of both study types (WJ).

Neuropsychological Testing

Neuropsychological evaluations were conducted under the supervision of a licensed psychologist according to guidelines established by the CSSCD [6]. Briefly, tests were administered to assess global intellectual functioning, behavioral adjustment, and specific motor function and coordination.

RESULTS (Table I and Fig. 1)

All six participants had small vessel disease demonstrable by MRI within the deep white matter and watershed areas of cortex. All six patients had abnormal neuropsychological testing. Four of the six also had large vessel disease demonstrated by MRA. One had cortical atrophy. In the two patients with isolated small vessel disease, neither MRA nor PET detected the small vessel lesion. For two of the four patients with both large and small vessel disease, PET detected a corresponding region of impaired glucose metabolism. When detected by PET, these metabolic lesions appeared more extensive than the anatomical lesion as imaged by MRI; a rim of hypometabolism was identified beyond the anatomic lesion as shown by MRI (Fig. 1).

DISCUSSION

In our study, four patients had a history of stroke due to large vessel obstruction. In two of the four, a corresponding, and more prominent, cortical lesion was detected by PET. This extended metabolic lesion in the absence of a fully corresponding anatomic abnormality suggests that a functional tissue deficit sometimes may

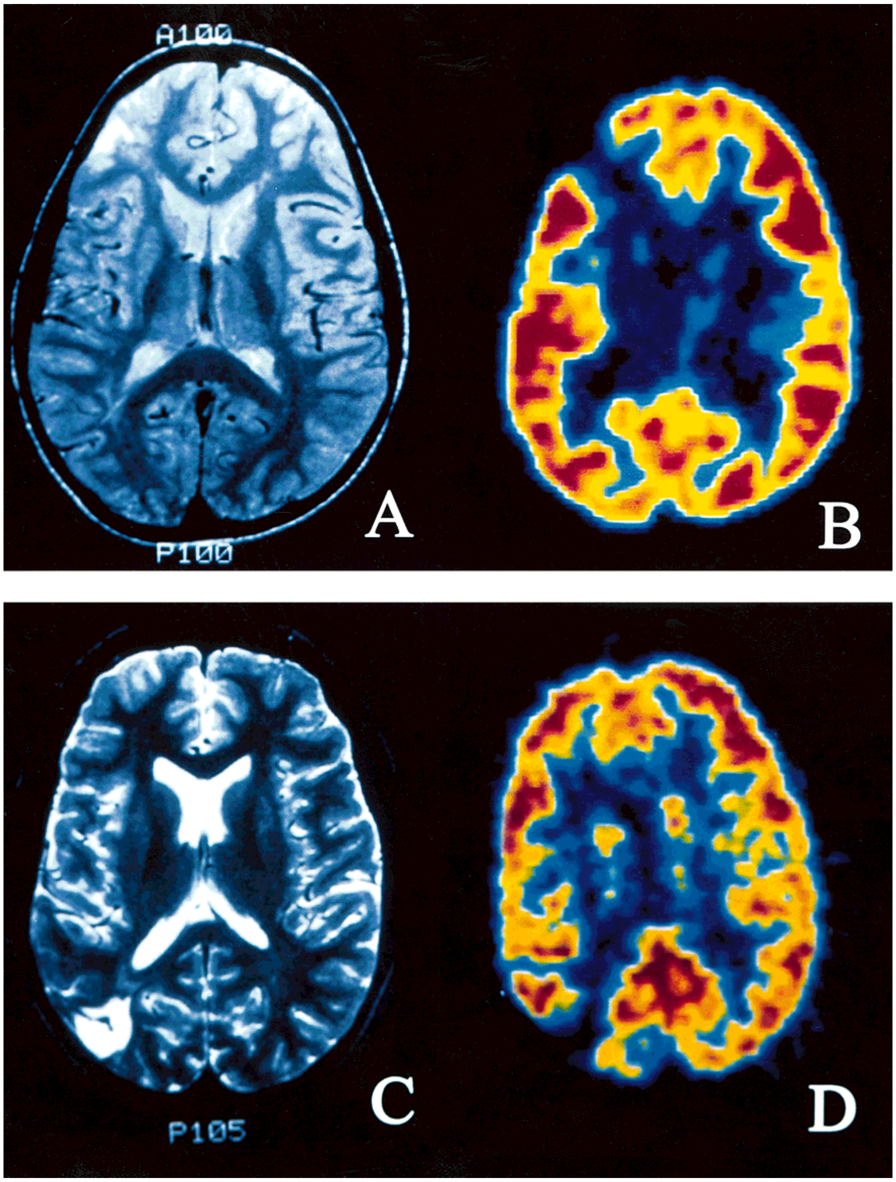

Fig. 1. Comparison of PET and MRI images for two subjects. (A) MRI shows deep white matter infarcts and infarctive lesion of the right frontal cortex. (B) PET shows a focal reduction in glucose metabolism occurring in the cerebral cortex of the right frontal lobe. (C) MRI demonstrates cystic encephalomalacia in the right parietal-occipital area in the distribution of a distal branch of the middle cerebral artery. Similar abnormalities are present in the left frontal region. These correspond to locations of previous hemorrhage. Mild atrophy is present. (D) PET demonstrates a single, larger area of focal hypometabolism in the right temporo-occipital area. Metabolic activity in other cortical regions and in the cerebellum is normal.

underlie a normal anatomic imaging study and persist despite chronic transfusion therapy. The finding is also consistent with the observation of poorly perfused penumbral tissue found by PET in adult stroke patients without SCD [14]. Such functional lesions may prove important in understanding the neurologic morbidity of SCD and could eventually play a role in its early recognition. The observation is also consistent with the diffuse frontal lobe hypometabolism noted by Rodgers et al. [13] in a series of six patients with SCD. However, in their study, subjects were neurologically normal and neither MRI nor neuropsychological evaluation was available for comparison.

Small infarcts of the deep white matter are among the most common lesions occurring in patients with SCD. They were present in all of our subjects though PET did not detect them with the presently used techniques. Since most of these lesions are small and in the white matter, failure to detect them may have resulted from both PET's intrinsically limited spatial resolution as well as the lower tissue-specific metabolic rates characteristic of white matter structures.

Limitations related to patient selection and technical factors are present in this study. Subjects were recruited on the basis of a prior neurologic event. While this design identifies individuals most likely to display an abnormality on PET, it precludes the observation of early or presymptomatic metabolic abnormalities. Also, the occurrence of stroke in a patient with SCD requires the prompt initiation of intensive long-term transfusion, a therapy that has profound effects on hemodynamics and arteriographic abnormalities [15]. The more technically chal-

TABLE I. Summary of Imaging Studies and Results of Neuropsychological Testing For Six Subjects With SCD Receiving Chronic* Transfusion Therapy for Previous Stroke

Age	MRI	MRA	NP	PET[a]
28RT	Multiple subcortical white matter lesions of the periventricular and centrum semiovale regions	50% narrowing of R internal carotid siphon	Verbal memory; expressive speech	Normal
23AP	Multiple deep white matter infarcts	NA	Multiple impairments	Normal
12KC	Small vessel involvement of the periventricular white matter and centrum semiovale	Normal	Verbal memory	Normal
10JW	Deep bilateral infarction of frontal lobes: L > R. Centrum semiovale moya-moya	NA	Verbal memory; expressive speech; multiple impairments	Normal
15JW	Posthemorrhagic cystic encephalomalacia and mild atrophy	Normal	Verbal memory; expressive speech; multiple impairments	R temporoparital hypometabolism
10GA	Lacunar infarct of L caudate head	R supraclinoid occlusion L supraclinoid stenosis	Multiple impairments	R frontal hypometabolism

*SCD, sickle cell disease; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; NP, neuropsychiatric; PET, positron emission tomography.
[a]PET studies read in blinded fashion.

lenging aspects of PET studies makes prompt evaluation difficult in the setting of acute stroke. An interesting population for this analysis could be drawn from the recently completed stroke prevention trial [7]. In this study, patients with large vessel obstructive disease identified by Doppler screening were eligible for entry. A baseline MRI and neurologic exam were performed. Individuals having large vessel disease defined by Doppler, but not yet on chronic transfusion therapy could be ideally suited to demonstrate a premorbid metabolic lesion in their distal cortical field, if such a phenomenon exists. It is only with stringent patient selection, and controlled clinical circumstances that the potential of PET neuroimaging in patients with SCD will be fully understood.

Finally, because nonquantitative PET imaging methods were used, global cortical hypometabolism cannot be excluded in these subjects. Additionally, the possibility exists of a secondary effect on adjacent gray matter metabolism, due to deafferentation from tissue damage at the time of stroke. If this were the case, more subtle differences in local tissue metabolism might have been obfuscated. Presently used methods of image acquisition were not optimized to compensate for these effects.

In summary, our study shows that, even in the setting of hypertransfusion, PET can detect central nervous system hypometabolism in some SCD patients with a history of large vessel infarctive stroke. However, the complexity of PET scanning, combined with its limited ability to detect known small vessel lesions will curtail its use as a screening test for neurologic abnormalities in SCD. Larger studies to better evaluate and compare imaging strategies are needed. At present, a combination of conventional imaging with neuropsychological testing remains the preferred evaluation for most SCD patients with neurologic symptoms.

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